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(12) **United States Patent**  
**Quaedflieg et al.**(10) **Patent No.:** US 7,595,408 B2  
(45) **Date of Patent:** Sep. 29, 2009(54) **METHODS FOR THE PREPARATION OF (3R,3AS,6AR) HEXAHYDRO-FURO[2,3-B]FURAN-3-OL**(75) Inventors: **Peter Jan Leonard Mario Quaedflieg, Waalre (NL); Bart Rudolf Romanie Kesteleyn, Berlare (BE); Robert Jan Vijn, Venlo (NL); Constantinus Simon Maria Liebregts, Helmond (NL); Jacob Hermanus Matheus Hero Kooistra, Haren (NL); Franciscus Alphons Marie Lommen, Horst (NL)**(73) Assignee: **Tibotec Pharmaceuticals, Ltd., Little Island, Co. Cork (IE)**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods for the preparation of diastereomerically pure (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol as well as a novel intermediate, (3aR,4S,6aS) 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one for use in said methods. More in particular the invention relates to a stereoselective method for the preparation of diastereomerically pure (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol, as well as methods for the crystallization of (3aR,4S,6aS) 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one and for the epimerization of (3aR,4R,6aS) 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one to (3aR,4S,6aS) 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one.

20 Claims, No Drawings